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Review

Post-traumatic vasospasm: Epidemiology, specificities, risk factors, and therapeutics

Clara Perrault[1], Audrey Melcus[1], Etienne Lefevre[2,3], Eimad Shotar[4], David Ditchi[1], Lamine Abdennour[1], Vincent Degos[1,3], Alice Jacquens[1,3,*]

[1] *Département d'Anesthésie Réanimation, Réanimation Neurochirurgicale, Hôpital de la Pitié Salpêtrière, Paris, France*
[2] *Service de Neurochirurgie, Hôpital de la Pitié Salpêtrière, Paris, France*
[3] *Sorbonne Université, Paris, France*
[4] *Service de Neuroradiologie, Hôpital de la Pitié Salpêtrière, Paris, France*

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ABSTRACT

Post-traumatic vasospasm (PTV) of intracranial arteries is a serious complication of traumatic brain injury (TBI) that can lead to significant neurological deficits and ischemic brain lesions. Despite its clinical relevance, the pathogenesis of PTV is not fully understood, and effective management strategies remain a challenge. This review aims to synthesize the current knowledge on pathophysiology, risk factors, detection, prevention, and treatment of PTV. Early detection of PTV is made difficult by the complexity of TBI and its management. The gold standard for vasospasm detection remains digital subtraction angiography (DSA). However, noninvasive techniques such as transcranial Doppler (TCD) and S100 protein monitoring may assist in detecting PTV. Compared with vasospasm associated with aneurysmal subarachnoid hemorrhage (aSAH), PTV appears to occur earlier and to resolve more quickly. Several risk factors have been identified, including the severity of TBI, younger age, SAH, or the presence of other hematomas. Treatment options include nimodipine and endovascular therapies, such as angioplasty and milrinone, though these require careful management due to their invasive nature and potential hypotensive effect. PTV represents a critical complication of TBI, requiring early detection and timely intervention to prevent secondary brain injuries. Although current strategies, such as nimodipine and intra-arterial therapies, have shown promise, further research is needed to refine these approaches and improve outcomes. Enhanced understanding of PTV's pathophysiology, along with the development of more effective diagnostic and therapeutic tools, is essential for advancing patient care in TBI.

Introduction

Vasospasm is a well-known complication of aneurysmal subarachnoid hemorrhage (aSAH). Over the past 60 years, studies have shown that cerebral vasospasm can occur following traumatic brain injury (TBI). However, this entity is less known and less tracked down by clinicians, even though delayed cerebral ischemia (DCI) is reported in 2.1%–12% of TBI[1,2] and vasospasm is one of the causes.

DCI is defined by the American Heart Association as "The occurrence of focal neurological impairment or a decrease of at least 2 points on the Glasgow Coma Scale. This should last for at least 1 h, should not be apparent immediately after aneurysm occlusion, and should not be attributable to other causes by means of clinical assessment, computed tomography (CT) or magnetic resonance imaging (MRI) scanning of the brain, and appropriate laboratory studies."[3] Imaging DCI is defined as "The presence of cerebral infarction on CT or magnetic resonance (MR) scan of the brain within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MR scan between 24 and 48 h after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarction from DCI."[4] DCI after TBI is rare, but it leads to poor functional outcomes and high mortality[2] by inducing ischemia in an arterial territory.

* Corresponding author: Alice Jacquens, Département d'Anesthésie Réanimation, Réanimation Neurochirurgicale, Hôpital de la Pitié Salpêtrière, Paris 75013, France and Sorbonne Université, Paris, 75013, France.
E-mail address: alice.jacquens@aphp.fr (A. Jacquens).

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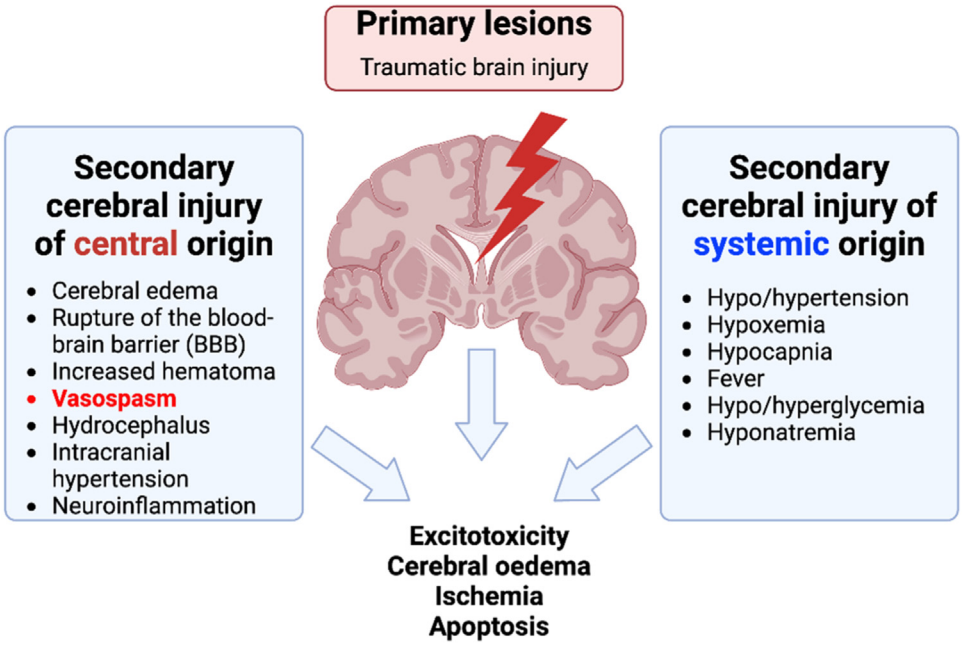

Figure 1. Secondary cerebral insult of systemic and central origin.

Each year worldwide, approximately 70 million individuals suffer from TBI,[5] 10 % of which are severe TBI (defined by a Glasgow Coma Scale [GCS] ≤8).[6] Moderate to severe TBI can lead to long-term poor functional outcomes, though precise statistics are lacking.[7–9] In the Transforming Research and Clinical Knowledge (TRACK)-TBI, 142 of 271 with severe TBI (52.4 %) and 54 of 72 with moderate TBI (75.0 %) achieved favorable outcomes (Glasgow Outcome Scale–Extended [GOSE] 4–8), also 19.3 % of the severe TBI patients and 32 % of the moderates TBI patients reported no disability at 1 year.[10]

TBI can lead to various primary lesions, including diffuse axonal injury, fractures, extradural hematoma, subdural hematoma, cerebral contusion or intraparenchymal hematoma, and subarachnoid hemorrhage, the latter is common after mild to severe TBI since it occurs in 33 % to 60 % of patients.[11,12]

The main objective in ICU after TBI is to prevent secondary brain insults from systemic and central origin, which are responsible for new lesions and are likely to affect the prognosis (Figure 1). The secondary brain insults of central origins encompass all potential consequences of the primary brain injury, including vasospasm.

All those secondary lesions are responsible for cerebral edema and ischemia, leading to intracranial hypertension and brain tissue destruction. Consequently, it is mandatory to know, detect, and treat those secondary lesions of both systemic and central origins.

Screening for vasospasm after TBI could potentially reduce mortality and improve outcomes. However, there are currently no established guidelines for preventing, screening, or treating post-traumatic vasospasm (PTV). This review aims to summarize current knowledge about PTV and to highlight the differences between PTV and aSAH-related vasospasm.

Cerebral Vasospasm in the Context of aSAH

Cerebral vasospasm is a well-known complication of aSAH, which accounts for 1 %–5 % of all strokes and is the third most common subtype of stroke.[13,14] Vasospasm occurs in 30 %–70 % of cases,[14–17] though it does not always result in DCI, which is seen in 17 %–40 % of cases.[16]

Cerebral vasospasm is defined as a prolonged but reversible narrowing of cerebral arteries typically beginning days after subarachnoid hemorrhage.[18] Clinical features such as fever, altered consciousness, worsening headaches, and/or focal neurological deficits can alert clinicians to the occurrence of vasospasm.[19] Vasospasm related to aSAH usually begins on the days 3–5 posthemorrhage, with a maximum narrowing occurring between days 5 and 14. It resolves gradually over 2–4 weeks.

Studies have sought to identify risk factors for vasospasm following aSAH, but the main risk factor seems to be the modified Fisher score and the Hijdra score,[20] which are both based on radiologic features. In addition, a history of smoking and hyperglycemia also seem to be risk factors for vasospasm after aSAH.[20,21]

Vasospasm and DCI lead to higher mortality and permanent neurological deficits.[22,23] Therefore, preventing, screening, and treating vasospasm represents a primary objective in the management of SAH after securing the aneurysm, as emphasized in the American Heart and Stroke Association Guidelines.[24] The guidelines recommend the use of calcium-channel inhibitors (nimodipine), to prevent the occurrence of vasospasm.

Recently, an inotropic drug that dilates vessels by phosphodiesterase inhibition (milrinone) has been used for DCI prevention, after aSAH, but it still requires further studies.[24–27] Other therapies will be detailed in the “Prevention and treatment of PTV” section.

Given the altered prognosis associated with symptomatic vasospasm following aSAH and its long-term consequences leading to morbidity and mortality, it seems essential to detect its occurrence after TBI. As vasospasm is an underdiagnosed complication of TBI, a deeper understanding of its mechanism, identification of risk factors, and knowledge of potential treatments

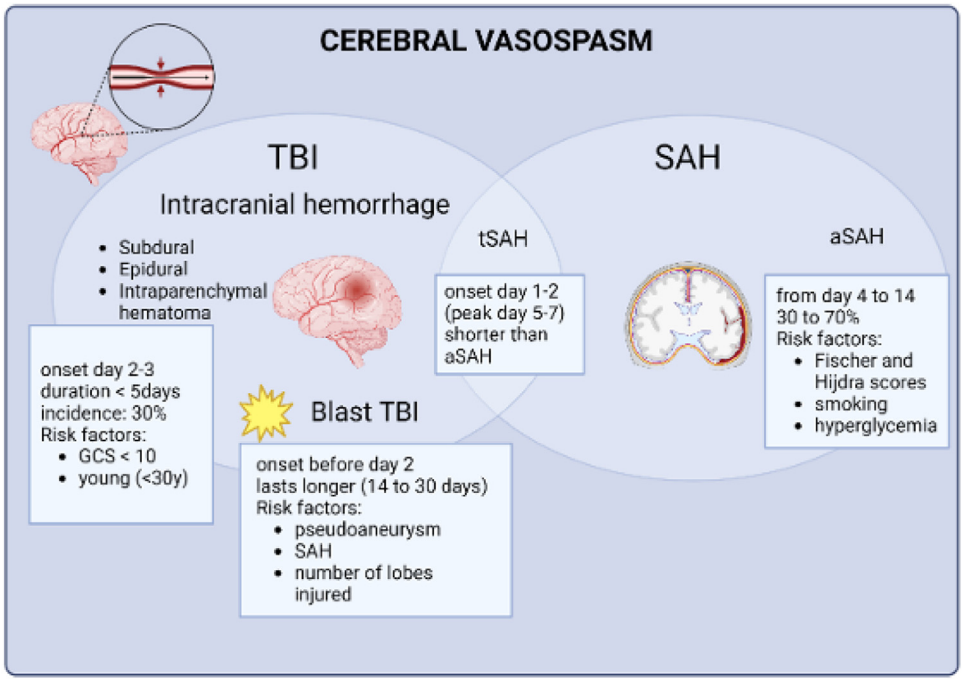

Figure 2. Different patterns of cerebral vasospasms.
aSAH: Aneurysmal subarachnoid hemorrhage; GCS: Glasgow coma scale; SAH: Subarachnoid hemorrhage; tSAH: Traumatic subarachnoid hemorrhage; TBI: Traumatic brain injury.

are essential to preventing further brain injuries (Supplementary Figure S1).

Unique Characteristics of Cerebral Vasospasm in the Context of TBI

PTV was first mentioned in the 1960s, yet its incidence remains unclear, varying from 25 % to 60 % of TBI (Figure 2).[28–31] In pediatric populations, the incidence ranges from 18 % to 45 %.[29] This significant variability can be attributed to differences in diagnostic tools, such as transcranial Doppler (TCD) (19 %–68 %) or angiography (18.6 %–41 %), as well as the diverse patterns of TBI and the heterogeneity of related studies.[32]

An important point is the variable pattern of PTV. Based on the multiple studies defining PTV, relying on vasospasm characteristics such as delay, duration, or associated risk factors, a division into 3 distinct groups seems to emerge, leading us to propose this classification: PTV related to traumatic SAH (tSAH), PTV not related to SAH (further subdivided into two subgroups: PTV following other intracranial hematomas and PTV following blast-related TBI).

PTV related to tSAH is very similar to the previously mentioned vasospasm seen after aSAH. Although some studies suggest that the presence of tSAH is a risk factor for PTV,[31] findings are inconsistent and a prospective study by Zubkov et al.[30] found no significant difference in the occurrence of vasospasm between TBI patients with SAH on their initial CT scan and those without SAH (37.9 % *vs.* 31.3 %, $P = 0.34$). However, when described in the literature, tSAH-related vasospasm occurs slightly earlier than aSAH-related vasospasm, typically around day 1 or 2, with a peak incidence between days 5 and 7.[29,30,33]

PTV due to other types of traumatic intracranial hemorrhage (intraparenchymal hematoma, extradural hematoma, subdural hematoma, and contusions) tends to occur earlier than aSAH-related vasospasm. There seems to be a difference in duration between PTV occurring in the anterior or posterior circulation. Indeed, PTV in the anterior circulation is described to last longer than in the posterior circulation, in either pediatric or adult populations.[28,29]

Clinically, diagnosing PTV is more challenging than diagnosing vasospasm following aSAH. Indeed, as previously reported in the literature, PTV tends to have a rapid onset, while a recent international survey of TBI in ICU (2023) revealed that sedations last <24 h in only 11 % of cases.[34] Furthermore, studies have shown that the severity of head trauma is a risk factor of PTV.[30,35] Thus, PTV often occurs in sedated patients, making it nearly impossible to detect clinical signs of neurological deficits during the initial phase. Therefore, it may be advisable to monitor the occurrence of vasospasm using TCD, a simple and noninvasive bedside examination routinely used in neurosurgical intensive care units.

If left untreated, vasospasm can lead to DCI, a complication of TBI that significantly increases the risk of mortality and severe disability.[35,36] One study showed that the risk of DCI after tSAH is approximately 17 %.[37] Thus, it is important to understand, screen, and treat PTV to prevent these severe outcomes.

Challenges in Early Detection of Vasospasm in the Context of TBI

Clinical examination of patients with TBI, multiple times a day is the primary method for detecting vasospasm. However, as noted, TBI patients are often sedated or in a coma, making clinical assessment challenging. Given this, it seems mandatory to actively search for the occurrence of PTV. TCD should be used daily after TBI for detecting vasospasm. This bedside monitoring allows screening of vasospasms. It is noninvasive, easy to learn, and easy to use daily.[38] It is recommended by the Guidelines of the American Stroke Association for aSAH.[24]

There is no specific recommendation about PTV detection, but aSAH-related vasospasm recommendations seem applicable

Table 1
Risk factors of vasospasm.

Risk factors	Authors	Population	Study design	Number of patients with PTV	Results
Young age (<30 years)	Perrein et al.[65]	Adult	Systematic review	NA	NA
	Dicpinigaitis et al.[109]	Adult	Retrospective study	375	OR=0.98, 95 % CI: 0.97 to 0.99
	Oertel et al.[33]	Adult	Prospective study	299	NA
Low admission GCS score (<10)	Perrein et al.[65]	Adult	Systematic review	NA	NA
	Dicpinigaitis et al.[109]	Adult	Retrospective study	375	OR=1.80, 95 % CI: 1.12 to 2.90
	Al-Mufti et al.[110]	Adult	Retrospective study	NA	NA
	Al-Mufti et al.[111]	Adult	Systematic review	NA	NA
	Oertel et al.[33]	Adult	Prospective study	NA	NA
Presence of subarachnoid hemorrhage	Perrein et al.[65]	Adult	Systematic review	NA	NA
	Martin et al.[40]	Adult	Prospective study	NA	NA
	Aminmansour et al.[66]	Adult	Cross-sectional study	NA	NA
	Dicpinigaitis et al.[109]	Adult	Retrospective study	375	NA
Intraventricular hemorrhage	Dicpinigaitis et al.[109]	Adult	Retrospective study	375	OR=6.27, 95 % CI: 3.49 to 11.26
Subdural, epidural hematomas	Zubkov et al.[30]	Adult	Prospective study	NA	NA
Hypokalemia	Dicpinigaitis et al.[109]	Adult	Retrospective study	375	OR=1.62, 95 % CI: 1.26 to 2.08
Smoking	Dicpinigaitis et al.[109]	Adult	Retrospective study	375	OR=1.36, 95 % CI: 1.02 to 1.80

CI: Confidence interval; GCS: Glasgow coma scale; NA: Not available; OR: Odds ratio; PTV: Post-traumatic vasospasm.

to PTV. Moreover, being able to detect vasospasm at the bedside, especially when patients are potentially hemodynamically unstable, offers a significant advantage.

Vasospasm has mostly been defined on the main cerebral arteries in most studies. Moderate vasospasm is defined in the literature as a mean blood velocity on the middle cerebral artery exceeding 120 cm/s and a Lindegaard index –a ratio between intracranial and extracranial velocities –greater than 3.[39] Severe vasospasm, as assessed by TCD, is defined as a mean velocity on the middle cerebral artery exceeding 200 cm/s.[29,33,36,40–43] The Lindegaard index is important to distinguish vasospasm from hyperemia, particularly in cases of suspected PTV, as hyperemia is often associated with TBI.

Hyperemia, defined as an increased cerebral blood flow, results in diffusely increased velocities in both intracranial and extracranial arteries. It typically occurs in the early stages of severe TBI and can induce brain swelling and intracranial hypertension.[44–46] Differentiating between hyperemia and cerebral vasospasm is essential, and the Lindegaard index is a valuable tool in making this distinction.

Although TCD is an easy and noninvasive method for detecting and monitoring vasospasm in at-risk patients (aSAH or TBI), the gold standard for vasospasm diagnosis remains digital subtraction angiography (DSA). This invasive diagnostic procedure not only allows the precise visualization of the vasospasm distribution but can also lead to local treatments.[47] Indeed, during vasospasm, endovascular treatments include chemical and mechanical arterial dilatations of the affected vessels.[48,49]

However, modern and noninvasive techniques have been developed for diagnosing vasospasm, such as computed tomography angiography (CTA) which provides a diagnostic accuracy of 90 % with a false-positive rate of 5 % when compared with DSA.[50,51] Its sensitivity for detecting vasospasm after symptoms onset is high (91 %).[52] Another noninvasive imaging technique, computed tomography perfusion (CTP), assesses abnormalities in cerebral perfusion following aSAH with high sensitivity and specificity and seems better at predicting which patients may require endovascular treatment.[53,54] In addition, CTP identifies patients at high risk of DCI after aSAH.[55]

Furthermore, another tool used in some centers to detect cerebral ischemia in aSAH-related vasospasm is the S100 protein, a calcium-channel binding protein. Elevated levels of S100 are associated with cerebral ischemia and worse GOSE outcomes.[56–58] A meta-analysis has established predictive thresholds for biomarkers related to imaging abnormalities on CT scans following mild TBI. For S100 protein, an optimal threshold of 0.72 μg/L after mild TBI achieves a sensitivity of 61 % (95 % confidence interval [CI]: 50 % to 72 %) and a specificity of 69 % (95 % CI: 64 % to 74 %), whereas the commonly used threshold of 0.1 μg/L yields a pooled sensitivity of 91 % (95 % CI: 87 % to 94 %) but a specificity of 30 % (95 % CI: 26 % to 34 %).[59] Daily monitoring of S100 protein seems to be helpful in detecting the occurrence of PTV, but many confounding factors can affect its dosage. Further studies are needed before this marker can be used on a daily basis.

Risk Factors for PTV

Risk factors associated with PTV are not yet well defined (Table 1). Head trauma is the leading cause of SAH,[60] and the presence of SAH is an independent factor associated with poor prognosis.[61–63]

However, even though it has been described, no correlation has been established between the size of the tSAH and the risk of PTV,[62] unlike aSAH for which the Fisher scale has been established.[64]

Although it was long believed that the presence of SAH was necessary for the development of vasospasm, numerous studies have since questioned this assumption. A correlation has also been demonstrated between the occurrence of PTV and the presence of epidural hematomas, subdural hematomas, intracerebral hemorrhages, and a low Glasgow score on admission.[30] In addition, young age has also been identified as a risk factor in several studies.[33,65] Indeed, in numerous studies, tSAH is associated with a high incidence of PTV, particularly in cases of severe head trauma.[66] The severity of the head injury itself evaluated by the Glasgow score is also recognized as an important risk factor for developing PTV.[30]

Prevention and Treatment of PTV

If not detected and treated promptly, PTV leads to a locoregional reduction of cerebral blood flow, ultimately causing DCI, which further increases the risk of death and disability.[24]

Therefore, the primary goals are to adequately prevent vasospasm and treat it when it occurs. Before the management of vasospasm was clearly defined, a study involving 2741 patients after aSAH revealed that 26 % of patients developed cerebral ischemia within six weeks, which was strongly correlated with poorer outcomes.[67] With modern aSAH management routines, the morbidity and mortality associated with vasospasm have been reduced to <10 %.[18]

Several therapies are recommended for vasospasm related to aneurysmal SAH. Those treatments have also been studied in the context of PTV and are detailed:

Triple-H therapy

In the context of aSAH-related vasospasm, triple-H therapy (hypervolemia, hypertension, and hemodilution) was once the leading approach for both prevention and treatment. However, this therapy has been abandoned in favor of maintaining normovolemia, with hypertension being the only "H" still recommended.[68] The reason for this shift is that hypervolemic hemodilution is associated with increased complications. The main complication is the reduction of brain tissue oxygenation,[68] but also hyponatremia, pulmonary fluid overload/edema, cardiac arrhythmia, congestive heart failure, cerebral edema, and excessive anemia.[69,70]

Given that triple-H therapy is no longer used in aSAH-related vasospasm, it is not recommended in patients after TBI, as it could exacerbate vasogenic edema.

Nimodipine

Nimodipine, a calcium-channel blocker, has demonstrated its effectiveness in improving neurological outcomes following aSAH and is recommended by the American Stroke Association in the prevention of vasospasm in all patients with aSAH.[24] The guidelines suggest using enteral nimodipine for 21 days,[24] though it can also be administered intravenously. A meta-analysis published in 2022 concluded that both enteral and intravenous nimodipine are similarly effective in preventing poor outcomes, DCI, and delayed ischemic neurological deficits.[71] In patients with aSAH, early initiation of enteral nimodipine is beneficial in preventing DCI and improving functional outcomes but does not reduce the incidence of vasospasm.[24]

Given the frequent occurrence of vasospasms after TBI, studies suggest the use of nimodipine for the prevention and treatment of PTV in patients with tSAH.[12,36] However, the results have been mixed, with some studies showing benefits and others highlighting risks. Vergouwen et al.[3] showed, in a systematic review, no beneficial effect of nimodipine on outcomes in patients with tSAH. Indeed, nimodipine can cause hypotension, which is particularly concerning in TBI patients with elevated intracranial pressure who require consistent cerebral perfusion pressure to avoid further brain infarction.[72]

A systematic review that included Head Injury Trials (HIT) I, II, and IV trials found no significant difference in poor outcomes between nimodipine and placebo (odds ratio [OR]=0.88, 95 % CI: 0.51 to 1.54), and no difference in mortality rates (OR=0.95; 95 % CI: 0.71 to 1.26).[3,72] In these studies, patients with tSAH were included. Nimodipine was introduced within 24 h of injury, in patients unable to obey commands, with dosages of 2 mg/h intravenously or 360 mg orally per day. The duration of treatment varied, with 7 days in HIT I and 21 days or more in HIT III.[72,73]

Currently, a Cochrane systematic review published in 2006 suggests that nimodipine may be beneficial in preventing PTV related to tSAH in a subgroup of patients with SAH-associated TBI, but it also highlights the potential adverse events and could be deleterious for some patients.[74]

Several studies have tried intrathecal treatment with calcium channel blockers to control cerebral vasospasm,[75] whether in the context of SAH[76] or TBI.[77] The results are conflicting, but it appears that this treatment, even if it could be effective on vasospasm, would promote the onset of ventriculitis.[75,78,79]

Endovascular therapy

Another recommended treatment for vasospasm after aSAH is balloon angioplasty or selective intra-arterial vasodilator therapy. Guidelines suggest this approach for patients with symptomatic cerebral vasospasm, particularly if they do not respond rapidly to hypertensive therapy.[80]

However, patients with TBI are often more challenging to transport to the angiosuit for such procedures due to hemodynamic instability or intracranial hypertension, which complicates maintaining them in a strict supine position on the angiosuit table.

Milrinone

Milrinone is a phosphodiesterase III inhibitor that increases cardiac output and causes vasodilation by preventing the breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).[81] Although milrinone is primarily used in cases of cardiogenic shocks, it has also been studied as a treatment of aSAH-related vasospasm.

In 2008, Fraticelli et al.[82] demonstrated the effectiveness and safety of intra-arterial milrinone (8 mg/artery) in reversing vasospasm after aSAH, with a 53 %±37 % increase in arterial diameter (P <0.0001). Shankar et al.[27] also showed significant angiographic improvement of vasospasm (P <0.0001) along with clinical improvement with milrinone (5 mg/artery), as only one out of 14 patients required repeated intra-arterial milrinone therapy.

A more recent controlled observational trial published in 2021 involving 94 patients with aSAH-related vasospasm found that intravenous milrinone was associated with a lower rate of endovascular angioplasty and appeared to positively impact long-term outcomes.[26] The Montreal Neurological Hospital developed a protocol for aSAH-related vasospasm, showing no significant deleterious effect using milrinone to treat vasospasm, over an 88-patient population.[83]

Although these studies suggest that intra-arterial and intravenous milrinone are safe and effective for treating DCI after aSAH, most of the research is based on retrospective case series or single-center cohorts. Larger, multicenter trials are needed to confirm these observations.[81]

In addition, all these studies focus on aSAH-related vasospasm. There is a lack of data regarding the use of milrinone in PTV. Two case reports suggest that milrinone may be safe and

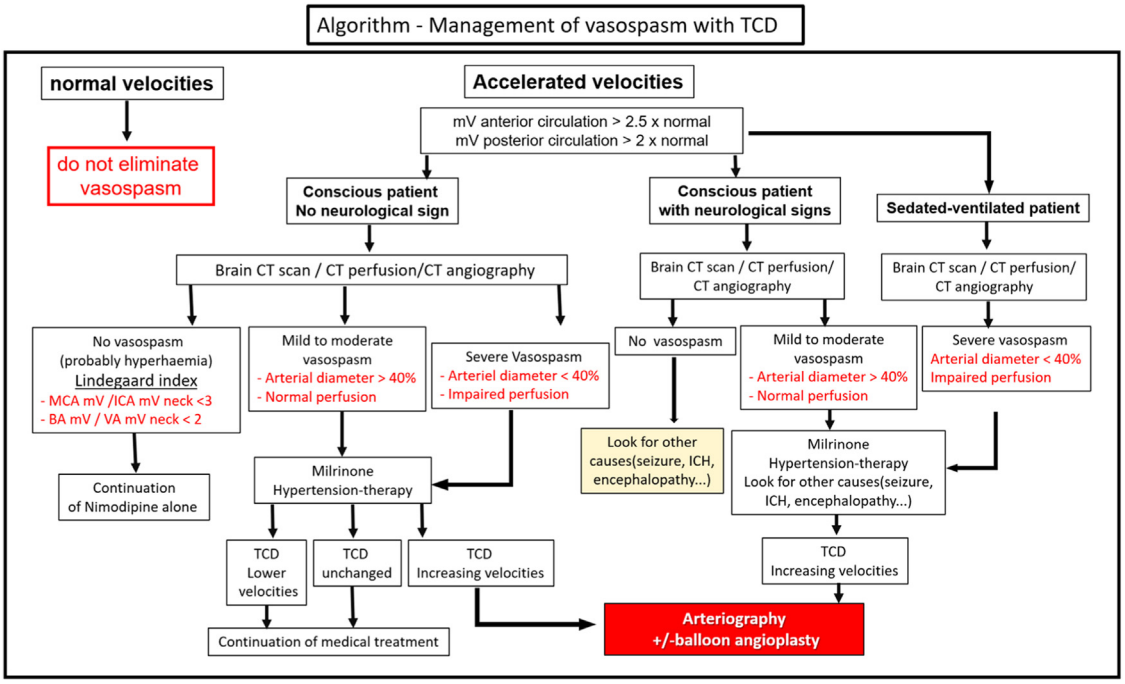

Figure 3. Suggestion for management of PTV detection and treatment.
BA: Basilar artery; CT: Computed tomography; ICA: Internal carotid artery; ICH: Intracerebral hemorrhage; MCA: Middle cerebral arteries; mV: Mean velocity; PTV: Post-traumatic vasospasm; TCD: Transcranial Doppler; VA: Vertebral artery.

potentially effective for treating PTV, especially when used in combination with nimodipine.[84] Further studies with stronger methodologies are necessary to validate Milrinone's use in PTV.

Clazosentan

Considering the potential role of endothelin-1 (ET-1) in the pathophysiology of PTV, clazosentan, an ET-1 receptor antagonist, has been studied in aSAH. Although it is a safe molecule that reduces the risk of vasospasm-related DCI, it does not improve neurological outcomes or mortality rates and is associated with adverse effects.[85–87] A meta-analysis highlighted these adverse effects, including pulmonary complications (RR=1.89; P <0.00001), hypotension (RR=2.47; P <0.00001), and anemia (RR=1.49; P < 0.0001).[88] The same meta-analysis found no significant decrease in mortality rates in the clazosentan groups. The phase 3 REACT trial, which tested clazosentan in aSAH did not meet its primary endpoint of preventing clinical deterioration.[89] As a result, this molecule is not recommended for aSAH-related vasospasm, and no studies have been published on its use in PTV.

Transfusion thresholds

Management of anemia is also important in TBI and for the prevention of vasospasm. In TBI, HEMOTION study, unfavorable outcomes, as measured on the Glasgow Outcome Scale-extended at 6 months, occurred in 68.4 % of the liberal strategy group (249 of 364 patients) and in 73.5 % of the restrictive strategy group (263 of 358 patients). Liberal transfusion strategy had a lower occurrence of an unfavorable outcome of 5.4 percentage points; however, results were negative because the study was powered to detect a 10 % difference.[90] In SAH, the secondary outcome in the SAHARA study showed a lower incidence of vasospasm in the liberal transfusion group, but no difference was seen in DCI.[91] A preplanned secondary analysis of the TRAIN study shows a significantly lower incidence of ischemia in the liberal transfusion group in patients with SAH.[92] Given all those aspects of diagnostic tools and possible treatments, we use in our service a flowchart to help manage this challenging issue (Figure 3).

Specific Aspects of PTV Pathogenesis

The pathophysiology of PTV is not yet fully understood (Table 2). A distinction must be made between the two main types of PTV: PTV with SAH and PTV without SAH.

Morphologically, PTV with SAH is similar to vasospasm following aSAH, with both conditions showing increased amounts of connective tissue in the subendothelial layer.[47]

PTV with SAH follows a model similar to aSAH model and involves several key mechanisms. Erythrocyte lysis due to blood clot formation in the subarachnoid space leads to the production of oxyhemoglobin, which induces direct vessel contraction by generating free radicals.[93,94] In addition, oxyhemoglobin captures nitric oxide, a crucial vasodilator, reducing its availability and leading to vasoconstriction.[95] Experimental studies have also shown the role of smooth muscle cells, where an intracellular increase in calcium concentration in spasmed arteries contributes to vessel contraction.[96] However, PTV can occur without the presence of blood in the subarachnoid space.

PTV pathophysiology remains debated but some hypotheses are highlighted in studies. Studies have shown that after an explosion, cellular stress generated by vessel stretching, leads to increased vessel contractility, notably through hypersensitivity to ET-1, and subsequent vascular remodeling.[97]

Table 2
Pathophysiology models of post-traumatic vasospasm.

Authors	Pathophysiological pathway	Model
PTV with SAH		
Kim-Shapiro et al.[95]	Oxyhemoglobin as a nitric oxide sensor	
Aoki et al.[93]	Oxyhemoglobin as an arterial vasoconstrictor	Rabbit cells *in vitro*
Bulter et al.[96]	Role of the calcium-dependent pathway for smooth muscle cell contraction in vasospasm	Dog cells *in vitro*
Steel et al.[94]	Free radicals' toxicity on muscle cells	Dog cells *in vitro*
Ide et al.[98]	Endothelin	Dogs *in vitro and in vivo*
Zimmermann et al.[99]		
PTV without SAH		
Alford et al.[97]	Cell-stress after blast	Humans *in vitro and in vivo*
Wang et al.[103]	Extramembrane vesicles due to cell apoptosis after TBI also have vasoconstrictor properties	Mice *in vitro*
Hariri et al.[112]	Increased production of eicosanoid (vasoactive principle) after TBI	Human cells *in vitro*
Kreipke et al.[104]	Calponine phosphorylation after TBI	Rat cells *in vitro*

PTV: Post-traumatic vasospasm; SAH: Subarachnoid hemorrhage; TBI: Traumatic brain injury.

ET-1, a potent vasoconstrictor, also plays a significant role in the pathogenesis of PTV. Its concentration correlates with hematoma volume and increases during vasospasm, supporting its involvement in the occurrence of PTV.[98,99] ET-1 has two receptor subtypes, ETrA and ETrB, which are located in different brain regions, including microvessels pericytes in the thalamus and hypothalamus, as well as various neural cell types. After moderate to severe TBI, the distribution of these receptors can change. Indeed, ETrA can be found in neurons, smooth muscle cells, and astrocytes, whereas ETrB is primarily located in neurons. This upregulation, along with an increased production of ET-1, both in plasma and cerebrospinal fluid, leads to altered cerebral blood flow. The interaction between ETrA and ET-1 is particularly correlated with the occurrence of PTV.[100,101] The increased transcription of protein-encoding ET-1 in pericytes located in microvessels is known to persist for about four hours, coinciding with the early onset of vasospasm after TBI.[65] A 1991 study conducted on dogs demonstrated that the administration of ET-1 induced growth in fibroblasts and vascular smooth muscle cells. However, this study found no significant correlation between ET-1 and cerebral vasospasm, as other vasoactive agents also included similar histological changes when administered at high doses.[102]

Additional mechanisms appear to be involved in head trauma. Studies have shown that after an explosion, cellular stress generated by vessel stretching leads to increased vessel contractility, notably through hypersensitivity to ET-1, and subsequent vascular remodeling.[97] Other studies have indicated that extracellular vesicles released during cell apoptosis after TBI also possess vasoconstrictor properties.[103]

Another protein, calponine (Cp), implicated in the regulation of smooth muscle contraction, might be involved in PTV. *In vitro*, this molecule is released from the cytosol after TBI, resulting in an increased expression of Cp during 48 h.[104]

A Specific Pattern of TBI: Blast Injury

Blast-induced TBI has been extensively studied, particularly in the context of military conflicts in Iraq and Afghanistan. Numerous experimental models have been developed to explore its pathophysiology, which remains incompletely understood.[105]

Blast-related injury is a unique form of trauma, defined by the United States Department of Defense as an "Injury that occurs as the result of the detonation of high explosives, including vehicle-borne and person-borne explosive devices, rocket-propelled grenades, and improvised explosive devices".[106] This injury is primarily due to the propagation of a shock wave following an explosion.

It is now recognized that blast-related TBI can be complicated by cerebral vasospasm. This specific type of vasospasm was studied by Armonda et al.[107] in 2006, who noted its early onset, around day 2, with an average duration of 14 days, though it can last up to 30 days. Several risk factors for the development of vasospasm after blast-induced TBI have been identified, including the presence of pseudoaneurysm, hemorrhage, and the number of lobes injured. Vasospasm is also highlighted as a factor that increases mortality. This same study analyzed the effects of blast-related TBI and PTV, which are associated with poor outcomes.[107]

In vitro and theoretical models have been employed to better understand the mechanism of cerebral vasospasm following bast-induced TBI, which may result from direct impact and mechanical stretch.[85] Alford et al.[97] using these models, demonstrated that a single rapid mechanical insult, similar to a blast, can induce vascular hypercontractility and remodeling, with ET-1 playing a significant role. Other growth factors, such as transforming growth factor (TGF)-β, have also been studied and are suggested to contribute to vascular contractility, leading to cerebral vasospasm.[108]

Conclusions

Vasospasm is a potentially severe complication of TBI, as it can lead to ischemic brain lesions. Diagnosing PTV is particularly challenging due to its early onset, especially since TBI often causes intracranial hypertension in the initial stages of care. Early screening for vasospasm following TBI is essential to prevent secondary injuries to an already compromised brain. In these conditions, bedside examinations are essential. Tools such as TCD, and monitoring of the S100 protein levels are very useful. Although SAH is a recognized risk factor for PTV, it is important to remember that it can occur following every type of TBI lesion. Although the risk factors are incompletely described, it is known that younger patients with severe TBI are at higher risk for developing PTV.[33] The challenges in treating PTV stem from the specific nature of TBI and the need to

manage or prevent intracranial hypertension. PTV presents significant challenges in terms of prevention, diagnosis, and treatment, and greater awareness is needed to prevent the occurrence of DCI.

CRediT Authorship Contribution Statement

Clara Perrault: Formal analysis, Investigation, Data curation. **Audrey Melcus:** Writing – original draft, Conceptualization, Data curation. **Etienne Lefevre:** Validation, Writing – review & editing, Data curation. **Eimad Shotar:** Writing – review & editing, Validation, Visualization. **David Ditchi:** Writing – review & editing, Conceptualization. **Lamine Abdennour:** Writing – review & editing, Validation. **Vincent Degos:** Supervision, Writing – review & editing, Conceptualization. **Alice Jacquens:** Writing – original draft, Conceptualization, Writing – review & editing, Supervision.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2025.05.004.

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